

REMARKS

Claims 35 and 47 are pending in the present case. Applicants note with appreciation that a number of prior objections and rejections have been withdrawn in view of the Amendment and Response filed on October 20, 2004.

In the Office Action mailed January 11, 2005, the Examiner has made several new rejections. Claims 35 and 47 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement with respect to showing possession of the invention, and under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the invention.

I. The inventors were in possession of the invention at the time of filing

Claims 35 and 47 stand rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement, with respect to showing possession of the invention (Office Action page 2).

The Examiner has raised specific questions about the terms "incomplete cleavage structure," and "signal exhibits a specific function as a matter of time, wherein said specific behavior as a function of time is indicative of the presence of said target nucleic acid." In particular, the Examiner has asserted that these terms are not supported by the present specification and are thus new matter. (Office Action page 3).

Without acquiescing to the Examiner's arguments and reserving the right to prosecute the original or a similar claim in the future, the claims have been amended to recite that "a second cleavage structure cleavable by said reagent is formed, said second cleavage structure comprising said cleaved unpaired region and a second probe oligonucleotide." The specification provides that an oligonucleotide released in a primary invasive cleavage reaction may be used as a component "to complete a cleavage structure to enable a secondary invasive cleavage reaction," and particularly provides for the formation of a second cleavage structure comprising a cleaved unpaired region derived from a first probe oligonucleotide and a second probe oligonucleotide. (see, *e.g.*, page 112, lines 11-14, page 116, lines 1-5, and Figure 96). As such, the specification discloses formation and cleavage of second cleavage structures and this term is not new matter.

The Examiner has also asserted that the specification does not support the term "signal exhibits a specific function as a matter of time, wherein said specific behavior as a function of time is indicative of the presence of said target nucleic acid." Without acquiescing to the Examiner's arguments and reserving the right to prosecute the same or similar claims in the future, Applicants have amended Claim 35 to recite that the "signal accumulates exponentially over time, wherein said exponential accumulation of signal over time is indicative of the presence of said target nucleic acid."

The specification teaches that products of the claimed reaction can accumulate over time. See, *e.g.*, page 169, lines 23-30 and page 171, lines 19-22. In addition, the specification teaches that the accumulation or yield of cleavage product, and therefore the signal, over time is exponential. See, *e.g.*, page 112, line 28 to page 113, line 7, which says explains that the yield of the first reaction step of the present invention has a yield Y , that is "the turnover rate, K , multiplied by the time of the reaction, t [i.e., $Y = (K)(t)$]." The yield of the sequential reactions of the present invention is expressed as Y^n , where n is the number of cleavage reactions that performed in the series. Because Y is the yield over time, Y^n is also a yield over time. As further explained in the specification (see, *e.g.*, page 117, line 28 to page 118, line 2), the accumulation of signal of the simple (non-sequential) assays is linear, while the accumulation of signal in the sequential cleavage reactions is exponential. Thus, the specification specifically teaches that the signal accumulates exponentially over time. Thus, this term is not new matter.

The present specification teaches each of the aspects of the presently claimed methods, showing that the inventors were in possession of the claimed invention at the time of filing and that these claims do not comprise new matter. Applicants therefore respectfully request that these rejections be withdrawn.

II. The claims are not indefinite.

Claim 35 stands rejected as vague and indefinite for the phrase "the cleaved unpaired region of the probe oligonucleotide and the reagent can come into contact with an incomplete cleavage structure to which the unpaired region of the probe oligonucleotide is capable of hybridizing to form a complex that can be, cleaved by the reagent to provide a product capable of being detected." The Examiner asserts that the first part of the phrase and the second part of the phrase to not correspond with each other. (Office Action page 5). Applicants assert that the

second part of the phrase follows from the first part of the phrase for the reasons provided in the Amendment and Response filed on October 20, 2004. Nonetheless, for business reasons, and without acquiescing to the Examiner's arguments, Claim 35 has been amended to recite "a second cleavage structure cleavable by said reagent is formed, said second cleavage structure comprising said cleaved unpaired region and a second probe oligonucleotide, and wherein said second cleavage structure is cleaved by the reagent to provide a detectable signal." As amended, the claim clarifies that a second cleavage structure is formed comprising the cleaved unpaired region derived from the first probe oligonucleotide and a second probe oligonucleotide. For explained above, each of these terms is supported by the specification and does not constitute new matter. For the reasons recited above, Applicants assert that the claims particularly point out and distinctly claim the subject matter of the invention such that the requirements of § 112 are met, and respectfully request that these rejections be removed.

New Claims

Claims 35 and 47 are pending in the present case. In the present amendment, new claims 62-84 are added. Claims 62-84 relate to methods for detecting a target polynucleotide. As claims directed to a method of detecting a target nucleic acid, these claims are consistent with the claims of Group I elected for prosecution in response to the Restriction Requirement mailed September 8, 2003.

In Office actions mailed on July 8, 2003 and January 5, 2004, the Examiner asserted that the then-pending claims comprised a number of distinct species. Applicants previously made the following species elections:

- Species 1, wherein the flap region of the invader oligonucleotide is capable of specifically hybridizing to the target polynucleotide;
- Species 6, wherein the determination of whether the signal exhibits a specific behavior as a function of time is performed in real time; and
- Species 10, wherein the second portion of the target polynucleotide is located immediately 5' to the first portion of the target polynucleotide.

New Claims 62-84 are readable on each of elected Species 1, 6, and 10.

Support for these claims is found throughout the specification. For example:

- Methods of detecting a target nucleic acid by forming a first and a second cleavage structure are discussed throughout the specification, including, *e.g.*, in Section IX, page 112, line 5 to 119, line 23;
- The detection methods of Claims 63-66 are described, *e.g.*, at page 13, lines 6-10, and page 66, lines 3-25; and
- 5' nuclease, including the thermostable 5' nucleases of DNA polymerases and FEN-1 nucleases, are discussed throughout the specification. See, *e.g.*, Examples 1, 16, 27, and 28.

All of the added claims are fully supported in the specification and do not comprise new matter.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all objections and rejections should be removed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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